providing at least one therapeutic agent to the blood to reduce adverse inflammatory mediator effects associated with treating an inflammatory mediator disease selected from the group consisting of systemic inflammatory response syndrome, multiorgan system dysfunction syndrome, multiorgan system failure and compensatory anti-inflammatory response syndrome; and

the therapeutic agent comprising activated protein C.

REMARKS

The Application has been reviewed in light of the Office Action mailed September 20, 2002. At the time of the Office Action, Claims 1-10 were pending in this Application. Claims 1-10 were rejected. To expedite allowance and further clarify the invention, Applicant has amended Claims 1, 3, 5 and 7 and added Claims 11 and 12 and respectfully requests reconsideration and favorable action in this case.

Rejections Under 35 U.S.C. §112

Claims 2 and 5-10 were rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.. Claim 2 and Claim 8 point out a "100 to 150 kiloDalton hemofilter." A Dalton is a unit of measurement defined as "an arbitrary unit of mass equal to 1/12 the mass of carbon 12 or 1.657×10^{-24} gram." (Taber's Cyclopedic Medical Dictionary, 17th Edition). It is a measurement of molecular weight frequently used in the field of biochemistry. A kiloDalton is one thousand Daltons. In the Claims it refers to the size of a particle that can pass through one pore of a filter. Claim 5 as amended particularly points out that the therapeutic agent is provided to the blood. Applicant respectfully traverses and submits that Claim 2 and 8 are allowable and Claim 5, as amended is allowable.

Rejections Under 35 U.S.C. §102

Claims 1-3, 5-6, and 8-9 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,287,516 issued to James R. Matson et. al. (hereinafter "Matson et al."). Applicant respectfully traverses and submits Matson et al. teaches an adsorptive device that "receives the stream of ultrafiltrate and selectively or nonselectively removes IM that cause

inflammatory mediator-related disease . . ." Matson et al. does not add a biologic agent to the blood. (col. 6, lines 35-38). Applicant teaches a therapeutic agent "provided to the filtered blood." Claims 1, 3 and 5 have been amended. Claim 2 depends from amended Claim 1. Claims 6, 8 and 9 depend from Claim 5. Applicant respectfully traverses and submits that Matson et al. does not anticipate Claims 1-3, 5-6 and 8-9 as amended.

Rejections Under 35 U.S.C. §103

Claims 4, 7, and 10 were rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Matson et al. as applied to Claims 1 and 5 above, and further in view of U.S. Patent No. 6,008,199 issued to Brian William Grinnell et al. (hereinafter "Grinnell et al."). Grinnell et al. teach a continuous infusion of activated protein C. (col. 9, lines 1-3) and define continuous infusion as a "continuing substantially uninterrupted the introduction of a solution into a vein . . ." (col. 9, lines 59-61). Matson et al. teach a hemofiltration system and an adsorbent device that selectively removes inflammatory mediators from the blood. (see Abstract). Applicant teaches providing a therapeutic agent, one of which is protein C, to the filtered blood into the tubing of a hemofiltration circuit. Grinnell et al. do not suggest combining the use of protein C with a method of hemofiltration. Claims 1, 5 and 7 have been amended. Claim 4 depends from Claim 1 and Claim 10 depends from Claim 5. Applicant respectfully traverses and submits that the Claims 4, 7 and 10, as amended, are allowable.

Claims 1, 2, 4-5, 7-8, and 10 were rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,193,681 issued to Alan Davidner et al. (hereinafter "Davidner et al.") in view of Grindell et al. Davidner et al. teach a method for killing microorganisms with ultraviolet radiation and removing target molecules. Davidner et al. do not teach providing a biologic agent to blood. Grindell et al. do not teach providing protein C to filtered blood and do not suggest combining hemofiltration to remove toxic mediators with providing a biologic agent to the blood. Claims 1, 5 and 7 have been amended. Claim 2 depends from Claim 1, Claim 4 depends from Claim 1, Claim 8 depends from Claim 5 and Claim 10 depends from Claim 5. Applicant traverses and respectfully submits that Claims 1, 2, 4-5, 7-8 and 10, as amended are allowable.

Claims 3, 6, and 9 were rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Davidner et al. in view of Grinnell et al. as applied to Claims 1 and 5 above, and further in view of U.S. Patent No. 5,523,096 issued to Thomas B. Okarma et al. (hereinafter "Okarma et al."). Okarma et al. teach a method of removing "selected factors" from the blood including pharmaceuticals, factors from blood components and selected factors that may be present in blood with septic shock syndrome. (Col. 1, Lines 17-30). Okarma does not suggest providing a therapeutic agent or other substance to the blood. Grinnell et al. teach a continuous infusion of protein C to a vein. Grinnell et al. to do not teach or suggest combining hemofiltration to remove toxic mediators with providing a biologic agent to the blood. Claims 3 and 5 have been amended. Claims 6 and 9 depend from Claim 5. Applicant therefore traverses and submits that Claim 3, 6 and 9, as amended, are allowable.

CONCLUSION

For the foregoing reasons, Applicant requests that the claims as amended be allowed. Applicant respectfully submits that amendments are supported by the Specification and add no new matter. Early and favorable acceptance of this Application is respectfully requested.

Attached hereto is a marked-up version of the changes made to the Claims by the current amendments. The attached pages are captioned **"Version with Markings to Show Changes Made."**

A two-month extension fee in the amount of $205.00 is submitted herewith with the Notification of Extension of Time. Also enclosed is a check in the amount of $42.00 for the filing fee for one new independent claim. (Although there are two new independent claims, one of the new independent claims is the third independent claim for this application and has no extra filing fee.)

Applicants do not believe there are any fees due, however, the Commissioner is hereby authorized to charge any fee or credit any overpayment to Deposit Account No. 50-2148 of BAKER BOTTS L.L.P.

BAKER BOTTS L.L.P.

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Enclosures: Notification of Extension of Time and check for filing fee

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IN THE SPECIFICATION

Please replace the paragraph beginning on Page 4, Line 3 with the following re-written paragraph:

As noted previously, the pro-inflammatory response is critical to host recovery and survival (by healing injury and eliminating infection), but when extreme this response causes vital organ dysfunction or failure. In biology, it is common for one response to be counter balanced by another response; these compensatory responses or systems allow restoration of balance and return the organism (e.g., the patient) to homeostasis. CARS is associated with the abatement of the **excess** **[excesses]** IM characteristic of SIRS, however CARS itself is often extreme and results in immune suppression. SIRS and CARS are each associated with respective characteristic IM. The immune suppression of CARS is very commonly associated with secondary infection. This secondary infection then elicits another SIRS, often worse and more destructive than the first. In patients, it is commonly this second episode of SIRS which is lethal.

Please replace the paragraph beginning on Page 6, Line 9 with the following re-written paragraph:

The detrimental mechanism of SIRS/MODS/MOSF and CARS **is** **[are]** the excessive activation of the inflammatory response. The inflammatory response consists of the interaction of various cell systems (e.g., **monocyte** **[onocyte]**/macrophage, neutrophil, and lymphocytes) and various humoral systems e.g., cytokine, coagulation, complement, and kallikrein/kinin). Each component of each system may function as an effector (e.g., killing pathogens, destroying tissue, etc.), a signal (e.g., most cytokines), or both. Humoral elements of the inflammatory response were known as toxic mediators, but are now known collectively as inflammatory mediators ("IM"). IM include various cytokines (e.g., tumor necrosis factor ("TNF"); the interleukins; interferon, etc.), various prostaglandins, **[e.g. PG 12) E2) Leukotrienes)]** various clotting factors (e.g., platelet activating factor ("PAF"), various peptidases, **[15]** reactive oxygen metabolites, and various poorly understood peptides which cause organ dysfunction (myocardial depressant factor ("MDF"). These compounds interact

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as a network with the characteristics of network preservation and self amplification. Some of these compounds, such as MDF and peptidases, are directly injurious to tissue; other compounds, such as cytokines, coordinate destructive inflammation. Infection (e.g., abscesses and sepsis) is a common complication of critical illness. Certain bacterial exotoxins, endotoxins or enterotoxins are extremely potent stimuli to SIRS/MODS/MOSF and CARS. The development and use of effective antibiotics and other supportive measures have not had a significant effect on the death rate from MOSF. The systemic inflammatory response with its network of systems (e.g., monocyte/macrophage, complement, antibody production, coagulation, kallikrein, neutrophil activation, etc.) is initiated and regulated through the cytokine ("CK") system and IM's. The CK system consists of more than thirty known molecules each of which activates or suppresses one or more components of the immune system and one or more CK in the network. The CK network is the dominant control system of the immune response. The sources of CK's are monocyte/macrophages and endothelial cells and they are produced in every tissue in the body. Key characteristics of the CK system are as follows: (i) CK are chemical signals coordinating immune system and associated system activities; (ii) commonly, two or more CK will trigger the same action providing a "fail safe" response to a wide variety of different stimuli (the systemic inflammatory response is critical to **an individual's** **[the individuals]** survival; these redundant control signals assure a system response which does not falter.); (iii) CK and IM concentrations (usually measured in blood) therefore increase in order to stimulate, control, and maintain the inflammatory response proportionally to the severity of the injury or infection; and (iv) as severity of injury or infection increases, the cytodestructive activity of the system increases resulting in MODS/MOSF. Therefore, high concentrations of CK and IM measured in the patient's blood, which are sustained over time, correlate with the patients risk of death.

Please replace the paragraph beginning on Page 9, Line 10 with the following re-written paragraph:

Also, of interest, note the existing technique of hemofiltration ("HF"), which was developed as a technique to control over hydration and acute renal failure in unstable ICU

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patients. Existing HF techniques may use a hemofilter of some sort, which consists of **[a]** cellulose derivatives or **a** synthetic membrane (e.g., polysulfone, polyamide, etc.) fabricated as either a parallel plate or hollow fiber filtering surface. Since the blood path to, through, and from the membrane is low resistance, the **[patients] patient's** own blood pressure drives blood through the filter circuit. In these HF applications, the hemofilter is part of a blood circuit. In passive flow HF, arterial blood flows through a large bore cannula, into plastic tubing leading to the filter; blood returns from the filter through plastic tubing to a vein. This is known as arteriovenous HF. Alternately, a blood pump is used, so that blood is pumped from either an artery or a vein to the filter and returned to a vein. This is known as **[pumped is]** arterio-venous HF or pumped veno-venous HF. Ultrafiltrate collects in the filter jacket and is drained through the ultrafiltrate line and discarded. Ultrafiltrate flow rates are usually 250 ml - 2000 ml/hour. In order to prevent lethal volume depletion, a physiologic and isotonic replacement fluid is infused into the patient concurrently with HF at a flow rate equal to or less than the ultrafiltrate flow rate. The balance of replacement fluid and ultrafiltrate is determined by the fluid status of the patient.

Please replace the paragraph beginning on Page 10, Line 7 with the following re-written paragraph:

The pores of most filter membranes allow passage of molecules up to 30,000 Daltons with very few membranes allowing passage of molecules up to 50,000 Daltons. The membranes used to treat renal failure were generally designed to achieve the following specific goals: (i) to permit high conductance of the aqueous phase of blood plasma water needed to permit the formation of ultrafiltrate at a fairly low transmembrane pressure (typically 20-40 m[,]mHg), which requires a relatively large pore size that incidentally passes molecules of up to 30,000 to 50,000 Daltons; and ii) to avoid passage of albumin (e.g., 68,000 Daltons). Note **that** with these existing hemofilters used to treat renal failure, the ultrafiltrate contains electrolytes and small molecules (e.g., urea, creatinine, and uric acid), but no cells and only peptides and proteins smaller than the membrane pore size. The composition of the ultrafiltrate is very similar to plasma water. Loss of albumin, and subsequently, oncotic pressure, could cause or aggravate tissue edema and organ dysfunction

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(e.g., pulmonary edema), so hemofilters are designed to avoid this by having molecular weight exclusion limits well below the molecular weight of albumin (e.g., 68,000 Daltons).

Please replace the paragraph beginning on Page 11, Line 13 with the following re-written paragraph:

Uncontrolled observations in ICU patients indicate that **HF [HT]**, in addition to controlling over hydration and acute renal failure, is associated with improvements in lung function and cardiovascular function. None of these improvements has been associated with **a** shortened course of ventilator therapy, **a** shortened ICU stay, or improved survival. The usual amount of ultrafiltrate **[taken] removed** in the treatment of over hydration and acute renal failure is 250 to 2000 ml/hour, 24 hours a day. A few published observations have suggested that higher amounts of ultrafiltrate brought about greater improvements in pulmonary and cardiovascular status; these have resulted in the development of a technique known as high volume HF ("HVHF). In HVHF, from 2 to 9 liters/hour of ultrafiltrate are taken for periods of from 4 to 24 hours or more. Furthermore, preliminary uncontrolled or poorly controlled studies suggest that HVHF improves survival in patients with SIRS/MODS/MOSF or CARS; there is growing interest in the use of HVHF in SIRS/MODS/MOSF and CARS. There is however great hesitance to use HVHF for the following reasons: (i) the high volumes (currently 24 - 144 liters/day) of ultrafiltrate require equally high volumes of sterile, pharmaceutical grade replacement fluid; at these high volumes, errors in measuring ultrafiltrate coming out and replacement fluid flowing into the patient could cause injurious or lethal fluid overload or volume depletion; (ii) the high volume of ultrafiltrate removed could filter out of the blood desirable compounds from the patient resulting in dangerous deficiencies; this is currently theoretical, but should be taken seriously; (iii) large volumes of warm (body temperature) ultrafiltrate flowing out of the patient, and large volumes of cool (room temperature) replacement fluid flowing into the patient can cause thermal stress or hypothermia; and (iv) high volumes of replacement fluid add considerable expense to the therapy.

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Please replace the paragraph beginning on Page 12, Line 19 with the following re-written paragraph:

HVHF, as currently practiced, uses conventional hemofilters with pore sizes which provide a molecular weight cut**off** of 30,000 Daltons and occasionally of 50,000 Daltons. The device and process described in United States Patent Number 5,571,418 generally contemplates the use of large pore hemofiltration membranes with pore sizes to provide molecular weight exclusion limits of 100,000 to 150,000 Daltons. With these higher molecular weight cutoffs, these membranes are designed to remove a wider range of different IM's; these large pore membranes should remove excess amounts of all known IM's. These large pore hemofiltration membranes have been demonstrated in animal studies to be superior to conventional hemofilter membranes in improving survival time in a swine model of lethal Staphylococcus aureus infection (Lee, PA et al. Critical Care Medicine, April 1998). It is anticipated that they will be superior to conventional membranes in SIRS/MODS/MOSF and CARS. However, it may be anticipated that in HVHF, the large pore membranes may also remove more **[different]** desirable compounds thus increasing the risk of the negative side effects of HVHF.

Please replace the paragraph beginning on Page 13, Line 10 with the following re-written paragraph:

Other techniques used in the past to treat acute renal failure and/or SIRS/MODS/MOSF and CARS include hemodialysis and plasmapheresis. Hemodialysis is well suited to fluid and small solute (less **[the]** **than** 10,000 Daltons) removal. However hemodialysis membranes remove very few IM (only those smaller **[the]** **than** 5000 to 10,000 Daltons) and so have been ineffective in improving **a patient's** **[patient]** condition in SIRS/MODS/MOSF and CARS. In the unstable ICU patient, hemodialysis commonly results in rapid deterioration of cardiovascular function and pulmonary function requiring premature termination of the dialysis procedure. Hemodialysis has also been associated with increasing the occurrence of chronic renal failure in survivors of SIRS/MODS/MOSF or CARS. HF was specifically developed (Kramer, 1997) to avoid these complications of hemodialysis and has been very successful in doing so.

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Please replace the paragraph beginning on Page 15, Line 16 with the following re-written paragraph:

In a particularized form the system further includes **a** 100 to 150 kiloDalton hemofilter.

Please replace the paragraph beginning on Page 15, Line 23 with the following re-written paragraph:

In a further particularized form, the system **[includes a]** includes a selective pharmaceutical agent to reduce adverse inflammatory mediator effects.

Please replace the paragraph beginning on Page 19, Line 12 with the following re-written paragraph:

The term "ultrafiltrate" refers to the filtered plasma water **, [and]** solute and molecules (including target peptides and proteins **[containing] including** IM) smaller than effective pore size of the membrane.

Please replace the paragraph beginning on Page 21, Line 12 with the following re-written paragraph:

FIGURE 1A is a schematic of the physical layout of various components of a preferred embodiment, including specimen or patient 100, hemofilter 102, blood pump 104, first ultrafiltrate pump 106a, second ultrafiltrate pump 106b, adsorptive device 108 having one or more chambers containing adsorbent material of one or more types, three-way stop cock or first three-way **[Joint] joint** 110, second three-way **[Joint] joint** 125, and associated tubing. FIGURE 1B is similar to FIGURE 1A, except that single ultrafiltrate pump 106 is used in lieu of first ultrafiltrate pump 106a and second ultrafiltrate pump 106b. Both FIGURES 1A and 1B position three-way stop cock or first three-way joint 110 in such a manner that it divides ultrafiltrate stream downstream from adsorptive device 108. FIGURE 2 is an alternate schematic of the physical layout of various components of a preferred embodiment shown in FIGURES 1A and 1B, except that three-way stop cock or first three-

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way joint 210 divides ultrafiltrate stream before adsorptive device 208. FIGURE 3 is a diagram showing the system flow of a preferred embodiment shown in FIGURE 1A. FIGURE 4 is a diagram showing the system flow of a preferred embodiment shown in FIGURE 2.

Please replace the paragraph beginning on Page 22, Line 3 with the following re-written paragraph:

Steps 301 and 302 (in FIGURE 3) and steps 401 and 402 (in FIGURE 4) show blood being continuously withdrawn from specimen or patient 100 (in FIGURES 1A and 1B) and specimen or patient 200 (in FIGURE 2) and directed to blood pump 104 (in FIGURES 1A and 1B) and blood pump 204 (in FIGURE 2) via first tubing 101 (in FIGURES 1A and 1B) and first tubing 201 (in FIGURE 2). Specifically, step 303 (in FIGURE 3) and step 403 (in FIGURE 4) show the continuous pumping of blood by blood pump 104 into hemofilter 102 via second tubing 103 (in FIGURES 1A and 113) and by blood pump 204 into hemofilter 202 via second tubing 203 (in FIGURE 2). Specimen or patient 100 (in FIGURES 1A and 1B) and specimen or patient 200 (in FIGURE 2), such as a human being, preferably have a major blood vessel cannulated allowing for the continuous withdrawal of blood by blood pump 104 (in FIGURES 1A and 1B) and blood pump 204 (in FIGURE 2). As shown in steps 304 and 306 (in FIGURE 3) and steps 404 and 406 (in FIGURE 4), hemofilter 102 **[ultra-filtrates]** **ultra-filters** blood extracted from specimen or patient 100 (in FIGURES 1A and 1B) and hemofilter 202 102 **[ultra-filtrates]** **ultra-filters** blood extracted from specimen or patient 200 (in FIGURE 2). And, step 305 (in FIGURE 3) and step 405 (in FIGURE 4) returns blood filtered by hemofilter 102 to specimen or patient 100 via third tubing 105 and fourth tubing 107 in FIGURES 1A and 1B and by hemofilter 202 to specimen or patient 200 via third tubing 205 and fourth tubing 207 in FIGURE 2.

Please replace the paragraph beginning on Page 22, Line 30 with the following re-written paragraph:

Referring to FIGURES 1A, 1B, and 2, ultrafiltration is a filtration process in which blood cells and blood proteins with a molecular size larger than the pore size of hemofilter

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membrane 109 (in FIGURES 1A and 1B) and hemofilter membrane 209 (in FIGURE 2) are retained in the blood path. The composition of hemofilter membrane 109 (in FIGURES 1A and 1B) and hemofilter membrane 209 (in FIGURE 2) are preferably comprised of biocompatible material, such as polysulfone, polyacrylonitrile, polymethylmethacrylate, polyvinyl-alcohol, polyamide, polycarbonate, cellulose derivatives, etc., but is not limited to these materials. The jacket of the hemofilter will be preferably comprised of a biocompatible material, such as polycarbonate, but not limited to, polycarbonate. Hemofilter membrane 109 (in FIGURES 1A and 1B) and hemofilter membrane 209 (in FIGURE 2) are preferably organized as a parallel plate membrane or as a membrane hollow fiber. Preferred embodiments use a hemofilter incorporating the techniques and materials discussed in United States Patent Number 5,571,418**[, which is herein incorporated by reference, which]** discusses the use of large pore hemofiltration membranes for hemofiltration processes. Hemofilter membrane 109 in FIGURES 1A and 1B and hemofilter membrane 209 in FIGURE 2 are preferably comprised of large pore hemofiltration membranes, which are preferably fabricated from any biocompatible material suitable for the purpose such as polysulfone, polyacrylonitrile, polymethylmethacrylate, polyvinyl-alcohol, polyamide, polycarbonate, cellulose derivatives, etc., but, of course, without limitation to these materials.

Please replace the paragraph beginning on Page 25, Line 15 with the following re-written paragraph:

Adsorptive device 108 (in FIGURES 1A and 1B) and adsorptive device 208 (in FIGURE 2) may have one or more chambers containing adsorbent material(s). The adsorbent material(s) is (are) preferably included within the respective adsorbent device and none will pass into the ultrafiltrate stream or return to specimen or patient 100 (in FIGURES 1A and 1B) and specimen or patient 200 (in FIGURE 2). The adsorbent materials used in the preferred embodiment may be coated or uncoated. The nature of the adsorbent materials used in the preferred embodiment is such that solutes to be adsorbed will be bound to the adsorbent materials. As shown in FIGURE 5A, 5B, and 5C, adsorbent material is presented to ultrafiltrate flow by structures such as rods or plates, or flows through structures such as beads or porous matrix of any configuration effective in presentation of adsorptive material(s)

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to ultrafiltrate stream, or flows through one or more chambers containing immobilized particulate, beaded or fragmented adsorbent material. Adsorbent materials may include, but are not limited to: silica, activated charcoal, nonionic resins, ionic resins, immobilized polymyxin B, anion exchange resin, cation exchange resin, neutral exchange resin, immobilized monoclonal antibodies, immobilized IM receptors, immobilized specific antagonists, cellulose and its derivatives, synthetic materials (e.g., polysulfone, polyacrylonitrile, polymethylmethacrylate, polyvinyl-alcohol, polyamide, polycarbonate, etc.) and the like or any combination **[thereof The]** **thereof. The** selection of adsorbent materials depends on the inflammatory mediators to be removed. Preferred embodiment uses polymyxin to remove endotoxin, anti-TNF antibody to remove TNF, polyacrylonitrile to remove interleukin 1-beta and TNF, among other adsorbents, both specific and nonspecific. Adsorbents may also be used in various combinations as the patients condition and stage of disease warrant.

Please replace the paragraph beginning on Page 34, Line 24 with the following re-written paragraph:

In one embodiment, a therapeutic agent may be a pharmaceutical agent developed to treat SIRS/MODS/MOSF and CARS. Pharmaceutical agents may include, but are not limited to, **[venerable]** allopurinol, elastase inhibitors, and prostaglandin inhibitors. Other pharmaceutical agents may be used as they are developed and become available. The pharmaceutical agent may be provided in a predetermined dosage amount such that, upon providing the pharmaceutical agent an effective amount of therapy is provided to a specimen or patient. In this manner, hemofiltration used in conjunction with a pharmaceutical agent reduces undesirable effects or disorders in an inflammatory response of a specimen or patient.

Please replace the paragraph beginning on Page 35, Line 15 with the following re-written paragraph:

In still another embodiment, the therapeutic agent may be a biological agent developed to treat SIRS/MODS/MOSF or CARS. Biological agents may include, but are not limited to, monoclonal antibodies or receptor antagonists such as anti-tumor necrolysis **or**

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necrosis factor, interleukin 1 receptor antagonist, and various endotoxin antibodies. Other biological agents may be used as they are developed and become available. The biological agent may be provided in a predetermined dosage amount such that, upon providing the biological agent, an effective amount of therapy is provided to a specimen or patient. In this manner, hemofiltration used in conjunction with a biological agent reduces undesirable effects or disorders in an inflammatory response of a specimen or patient.

Please replace the paragraph beginning on Page 37, Line 25 with the following re-written paragraph:

Additionally, in a preferred embodiment therapeutic agent 730 may provide variable dose adjusted pharmaceutical agents and/or biological agents as needed by specimen or patient 700. In one embodiment, a therapeutic agent may be a pharmaceutical agent developed to treat SIRS/MODS/MOSF and CARS. Pharmaceutical agents may include, but are not limited to, **[venerable]** allopurinol, elastase inhibitors, and prostaglandin inhibitors. Other pharmaceutical agents may be used as they are developed and become available. The pharmaceutical agent may be provided in a predetermined dosage amount such that, upon providing the pharmaceutical agent an effective amount of therapy is provided to a specimen or patient.

Please replace the paragraph beginning on Page 38, Line 8 with the following re-written paragraph:

In another embodiment, the therapeutic agent may be a biological agent developed to treat SIRS/MODS/MOSF and CARS. Biological agents may include, but are not limited to, monoclonal antibodies or receptor antagonists such as anti-tumor necrolysis **or necrosis** factor, interleukin 1 receptor antagonist, and various endotoxin antibodies. Other biological agents may be used as they are developed and become available. The biological agent may be provided in a predetermined dosage amount such that, upon providing the biological agent, an effective amount of therapy is provided to a specimen or patient. Therefore, as different types or new therapeutic agents become available, the system illustrated in FIGURE

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7 may be configured to provide the newly available therapeutic agents with hemofiltration thereby providing an enhanced therapy of SIRS/MODS/MOSF and CARS.

IN THE CLAIMS

Please amend Claims 1, 3, 5, and 7 and add new Claims 11 and 12 as follows:

WHAT IS CLAIMED IS:

1. (Amended) A hemofiltration system for treating inflammatory mediator related diseases, the system comprising:

a hemofilter **operable** to receive blood from a specimen **[the hemofilter removing] and to** selectively **remove** inflammatory mediators from the blood; **[and]**

at least one therapeutic agent used in association with the hemofilter **to treat an inflammatory mediator disease selected from the group consisting of systemic inflammatory response syndrome, multiorgan system dysfunction syndrome, multiorgan system failure and compensatory anti-inflammatory response syndrome; and**

the therapeutic agent **operable** to reduce adverse inflammatory mediator effects.

3. (Amended) The system of Claim 1, wherein the at least one therapeutic agent comprises a **[selective]** biological agent **selected from the group consisting of monoclonal antibodies, anti-tumor necrosis factor, interleukin 1 receptor antagonist and endotoxin antibodies** to reduce adverse inflammatory mediator effects.

5. **(Amended)** A method for treating inflammatory mediator related diseases, the method comprising:

receiving blood from a specimen;

filtering the blood using a hemofilter, **[the hemofilter removing] to remove** selective inflammatory mediators from the blood; and

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providing at least one therapeutic agent **to the blood** **[the therapeutic agent reducing]** **to reduce** adverse inflammatory mediator effects **associated with treating an inflammatory mediator disease selected from the group consisting of systemic inflammatory response syndrome, multiorgan system dysfunction syndrome, multiorgan system failure and compensatory anti-inflammatory response syndrome.**

7. **(Amended)** The method of Claim 5, wherein the therapeutic agent comprises a pharmaceutical agent **selected from the group consisting of allopurinol, elastase inhibitors and prostaglandin inhibitors**.

11. **(New) A hemofiltration system for treating inflammatory mediator related diseases, the system comprising:**

a hemofilter operable to receive blood from a specimen and to selectively remove inflammatory mediators from the blood;

the hemofilter comprising a 100 to 150 kiloDalton hemofilter;

the hemofilter associated with an adsorptive device;

at least one therapeutic agent used in association with the hemofilter to treat an inflammatory mediator disease selected from the group consisting of systemic inflammatory response syndrome, multiorgan system dysfunction syndrome, multiorgan system failure and compensatory anti-inflammatory response syndrome;

the therapeutic agent operable to reduce adverse inflammatory mediator effects; and

the therapeutic agent comprising activated protein C.

12. **(New) A method for treating inflammatory mediator related diseases, the method comprising:**

receiving blood from a specimen;

filtering the blood using a hemofilter to remove selective inflammatory mediators from the blood;

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providing at least one therapeutic agent to the blood to reduce adverse inflammatory mediator effects associated with treating an inflammatory mediator disease selected from the group consisting of systemic inflammatory response syndrome, multiorgan system dysfunction syndrome, multiorgan system failure and compensatory anti-inflammatory response syndrome; and

the therapeutic agent comprising activated protein C.